Update on Cognition

CNTRICS: Bringing Clinical Treatment Trials Closer to the Brain

by Philip D. Harvey, PhD

INTRODUCTION

The NIMH has been funding research initiatives with lots of catchy acronyms in the last few years, like CATIE, STEP-BD, MATRICS, and TURNS. We have discussed several of the cognitively oriented ones in this column, and there is a new one worth learning. The Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia, or CNTRICS[1], is an NIMH-sponsored initiative that takes the sophisticated cognitive neuroscience tools that have proliferated in the past decade and turn them toward drug discovery, development, and eventual improvements in treatments for schizophrenia.

COGNITIVE NEUROSCIENCE OF SCHIZOPHRENIA

The combination of high-resolution functional magnetic resonance imaging (fMRI), time-linked electroencephalogram (EEG) technology, and clear thinking about cognitive constructs has led to a number of advances in understanding brain dysfunction in schizophrenia and where a number of old findings have been put under a new light. For example, rather than attempting to identify tests sensitive to regional brain dysfunction through the trial and error process of administering tests to patients with large (and often nonspecific) brain lesions, changes in regional brain activation associated with subtle manipulations of cognitive processing demands can be directly quantified. Thus, the response of regions of the brain to subtle manipulations of cognitive demands can be visualized with greater precision than previously, making the evaluation of "regional brain dysfunction" a meaningful statement.

Further, using these sophisticated experimental manipulations and imaging techniques can sharpen the resolution with which neurobiological phenomena can be evaluated. For instance, it has been known since the advent of neuroimaging technology that people with schizophrenia manifest reduced frontal cortical activation, referred to as "hypofrontality," when performing cognitively demanding tasks. Using a task that manipulated the difficulty of a spatial working memory procedures,

frontal-lobe dependent cognitive operation, Callicott, et al.[2] was able to show that the changes in brain activation seen were not reflective of some specifically "schizophrenic" trait. Rather, they demonstrated that healthy people showed "hypofrontality" under conditions of cognitive processing overload, which for the healthy people was at a considerably higher level of processing demand than for the people with schizophrenia. The cortical activation previously seen in people with schizophrenia at lower levels of processing load was essentially indistinguishable from the activity of healthy people at higher load levels. As a result, the response of the brain to information processing load across both ill and healthy people was instantly better understood.

WHAT IS THE PURPOSE OF CNTRICS?

MATRICS has led to the development of a consensus cognitive battery—the MATRICS consensus cognitive assessment battery (MCCB)—to be used in clinical treatment studies of novel pharmacological treatments for cognitive dysfunction in schizophrenia and is currently identifying additional "co-primary" measures (as described in the December column of *Psychiatry 2007*)[3] for use in these same types of trials. The elements of the MCCB met a high standard of professional consensus and empirical validation and all were standard neuropsychological (NP) tests in wide clinical use prior to the MATRICS initiative. However, standard NP tests were never designed to be specific to the functions of any one brain region nor were they designed to measure a single, easy-to-manipulate, cognitive process. Thus, while standard NP tests are undeniably functionally relevant and widely sensitive to impaired cognitive performance (hence very clinically useful), they are not likely to be useful as tools to identify new cognitive targets, processes, or regional brain dysfunctions in a way that will advance new drug discovery. Behind CNTRICS is the notion that increased specificity of measurement in clinical trials will lead to more rapid advances in the broad therapeutic domain of cognition and disability in schizophrenia.

...while standard NP tests are undeniably functionally relevant and widely sensitive to impaired cognitive performance (hence very clinically useful), they are not likely to be useful as tools to identify new cognitive targets, processes, or regional brain dysfunctions in a way that will advance new drug discovery.

WHY IS AN INITIATIVE NEEDED?

While standard NP assessments have been used in studies of cognitive enhancing effects of medications since the early studies of amphetamine in ADHD, cognitive neuroscience is an emerging area. Standard NP tests have been commercially available for over 50 years. In contrast, CN tests are not actually tests in most cases; they are better characterized as "procedures." Stimulus parameters, presentation of the stimuli, response variables collected, and populations studied have often varied widely from procedure to procedure, within procedures, and from laboratory to laboratory. Many of these procedures are run with sophisticated customized software on computers that have themselves been modified from the standard commercial versions. Often the testers who administer the assessment are the same research technicians who developed some elements of the procedure, and often the administration of the tests is quite complex. In addition, there has been little attention paid on the part of many CN researchers to the kinds of systematic demographic influences on performance with which clinical neuropsychologists are (over)concerned. For instance, systematic studies of the influence of age, education, ethnicity, and gender are typically lacking in the CN domains, and many of the data on healthy controls have been collected on highly educated college students whose motivations to perform may be different from those in a clinical trial. Thus, there are essentially no "out-of-the-box", "off-the-shelf" CN tests that can be adapted to use in clinical trials in the way that standard NP tests were adapted in the 1990s for studies of atypical antipsychotic medications.

STANDARDIZATION IN TRIALS

One of the hallmarks of clinical trials is adoption of a systematic approach with high levels of standardization aimed at replicability of the findings. And one of the hallmarks of cognitive neuroscience research is innovation: Each lab or site works to improve on methods and technology to more closely capture the scientific construct in which it is interested. Each uses the latest in imaging technology to identify increasingly more subtle variations in

brain structure or function that correlates with performance. Thus, there are often multiple versions of test procedures aimed at the same construct in different laboratories and these procedures may only work on a single computer system. This is not likely to be a method that can be directly translated to wide-ranging research efforts.

Standardization has many features, and standardization alone is not necessarily an impediment to innovation. Standardization includes systematizing the instructions to research participants, test stimuli, and the recording of responses. Much like the application of standardized clinical methods to diagnosis of mental illness (such as the Structured Clinical Interview for DMS Disorders [SCID]) has led to a highly reliable (but maybe not completely valid) diagnostic system, similar standardization in psychological assessments allows for the application of these tests across different test administrators. Much like laboratory blood values for a metabolic panel, the results of standardized psychological tests are interpretable across test administrators and testing sites.

Another element of the development of standardized methods is that of the development of "normative standards." This means, quite simply, that a raw score is converted into a score that informs as to where that score stands in terms of the performance of other members of the general population. An example is the standard IQ test, where a score that is consistent with the average of the general population of people of the same age is 100. The standard deviation is 15. Thus, a person with an IQ of 85 is as much below average as someone with an IQ of 115 is above. No clinician looks at raw IQ test data; they all examine and understand normed scores.

The norming process is obviously complex and requires assessment of large numbers of healthy people. Often CN tests have no such data available, both because of narrow use of the test and minimal interest on the part of investigators in these broader uses. As a result, there is no information for many of these procedures as to whether a given score is at or lower than expectations, based on education or age. Changes in scores based on an intervention could not be interpreted in terms of how large the improvement is and whether it has any clinical meaning. Similarly, most standardized psychological tests are performed better by younger and more highly educated people. Since most CN data have been collected on highly educated younger people (often college students), then it is not clear if these tests would even be feasible to administer to older, sicker, and less educated populations.

Much like laboratory blood values for a metabolic panel, the results of standardized psychological tests are interpretable across test administrators and testing sites.

THE GOALS OF CNTRICS

The goal of CNTRICS is to take these CN procedures that are specific and sensitive to brain function and dysfunction and turn them into psychological tests. This is achieved by standardizing the procedures, conducting feasibility studies in diverse healthy samples, understanding the influence of various demographic factors on performance, and the initial development of normative standards in order to better understand the meaning of scores on the tests. The hope is that the next generation of clinical treatments could then be informed by outcomes measures that are more closely proximal to brain function than the current group of standardized tests, but a standardized and potentially sensitive to changes in functioning.

REFERENCES

1. Carter CS, Barch DM. Cognitive neuroscience-based approaches to measuring and improving treatment effects on cognition in schizophrenia: the CNTRICS initiative. *Schizophr Bull* 2007;33:1131–7.
2. Callicott JH, Mattay VS, Bertolino A, et al. Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. *Cereb Cortex* 1999;9:20–6.
3. Harvey PD. The latest developments in the MATRICS initiative. *Psychiatry* (Edgemont) 2007;4(12):29–31.

AUTHOR AFFILIATION: Dr. Harvey is Professor of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia.

ADDRESS CORRESPONDENCE TO: Philip Harvey, PhD, Professor of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Woodruff Memorial Building, 101 Woodruff Circle, Suite 4000 Atlanta, GA 30032; E-mail: philipdharvey1@cs.com